Treatment Continuity and Bone Marrow Suppression in Whole-Brain and Whole-Spinal Cord Radiotherapy for Medulloblastoma Patients

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Zongtai Li*, Zhiyue Lin*, Hui Liu*, Runnan Xiao, Chuyan Lin, Wenlong Zhu, Jiaxiu Luo, Senku Xu, Feng Chi and Huilang He
Department of Radiotherapy, State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-sen University Cancer Center, Guangzhou, China.

ABSTRACT

BACKGROUND: This study investigated the factors influencing treatment continuity and bone marrow suppression in whole-brain and whole-spinal cord radiotherapy for medulloblastoma, providing a clinical reference for mitigating the impact of hematological suppression on radiotherapy continuity.

METHODS: A retrospective analysis was conducted on patients with medulloblastoma who underwent craniospinal irradiation (CSI) radiotherapy at our hospital between August 2019 and December 2023. According to the inclusion and exclusion criteria, a total of 87 patients were enrolled. The bone marrow suppression status, clinical data, and radiotherapy dose data of the enrolled patients were recorded, and correlation analyses were performed. Based on the correlation results, further group comparisons were subsequently conducted.

RESULTS: Overall, 22.99% (20 out of 87) of the patients experienced treatment interruption (median duration, 6.5 [5, 8] days), typically during the 12th (7.5, 14.75) radiotherapy session. Treatment continuity was weakly correlated with age and treatment modality, and the timing of interruptions was weakly correlated with dosage and treatment modality. Bone marrow suppression severity was weakly correlated with age, body mass index (BMI), and treatment modality. Treatment modality and age were found to be independent predictors of treatment continuity and the degree of bone marrow suppression, respectively. Subgroup comparisons revealed differences in the severity of bone marrow suppression, grade of hematological toxicity, and timing of interruption depending on the treatment modality, dosage, and sex ($P < .05$).

CONCLUSIONS: Timely monitoring of hematological changes, especially in the middle and posterior segments after radiotherapy, is crucial. Treatment with helical tomotherapy, male sex, younger age, and lower BMI during radiotherapy are indicators of greater clinical attention.

KEYWORDS: Medulloblastoma, whole-brain and whole-spinal cord radiotherapy, continuity, bone marrow suppression, associated factors

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CORRESPONDING AUTHORS: Senku Xu, Department of Radiotherapy, State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-sen University Cancer Center, 651 Dongfeng Road East, Guangzhou 510060, Guangdong, China. Email: xusk@sysucc.org.cn

Feng Chi, Department of Radiotherapy, State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-sen University Cancer Center, 651 Dongfeng Road East, Guangzhou 510060, Guangdong, China. Email: chifeng@sysucc.org.cn

Huilang He, Department of Radiotherapy, State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-sen University Cancer Center, 651 Dongfeng Road East, Guangzhou 510060, Guangdong, China.
Email: hehl@sysucc.org.cn

Introduction

Medulloblastoma (MB), the most common malignant brain tumor in children, is an embryonal malignant tumor arising from early neuroepithelial cells in the cerebellum. The standard treatment for MB involves surgery combined with craniospinal irradiation (CSI) and adjuvant chemotherapy.[1,2] CSI involves prophylactic irradiation of the entire brain and spinal cord, with a relatively high dose (boost) to the posterior fossa. However, the complex and extensive irradiation of tissues, particularly the spinal cord, leads to adverse reactions.[3,4] Hematological toxicity is a common adverse reaction to CSI that influences the continuation of whole central nervous system radiotherapy, affecting the overall treatment outcome.[5,6] In China, the most commonly used CSI strategies at present are helical tomotherapy (HT), three-dimensional conformal radiotherapy, and intensity-modulated radiotherapy (IMRT).[7] This study explored the relationships between bone marrow suppression and patient characteristics, including sex, age, body mass index (BMI), tumor stage, tumor location, treatment modality, chemotherapy status, and continuity of radiotherapy, to clarify their impacts on treatment outcomes and guide the implementation of timely interventions during radiotherapy to benefit patients.

Materials and Methods

Inclusion and exclusion criteria

Medulloblastoma patients admitted to the Cancer Prevention and Treatment Center of Sun Yat-sen University from August 2019 to December 2023 were selected for screening. The

*Zongtai Li, Zhiyue Lin, and Hui Liu contributed equally to this work.

inclusion criteria included preradiotherapy assessments of liver and kidney functions and routine blood test results by the attending physician, a Karnofsky performance score (KPS; electrocorticography [ECOG]-Scoring criteria proposed by the Eastern American Cooperative Oncology Group) ⩾ 70, completion of the radiotherapy plan, first experience of undergoing radiotherapy, and compliance with radiotherapy. The exclusion criteria were intolerance to radiotherapy, severe organ-related diseases, and cognitive or consciousness impairments. This study was approved by the Ethics Committee of Sun Yat-sen University Cancer Center (approval no. B2023–608–01).

Instrumentation

Positioning was performed using a Philips Brilliance 16-slice large-aperture spiral computed tomography (CT) simulator (Philips, Netherlands). Patients in the HT, IMRT, and three-dimensional conformal radiation therapy (3D-CRT) groups were administered radiotherapy with a Tomotherapy Hi-Art accelerator (accuracy, USA), Varian Unique linear accelerator (Varian, USA), or Elekta Synergy linear accelerator (Elekta, Sweden), respectively.

Data acquisition and processing

As described previously, patients were stratified by CSI dose into standard- (23.4 Gy) and high-risk (36 Gy) groups. The standard-risk group received a reduced dose of CSI (clinical target volume [CTV]-brain and CTV-spine) of 23.4 Gy, 1.8 Gy per dose, once a day for 13 fractions. In the high-risk group, the CSI dose was 36 Gy once a day (1.8 Gy each time), for a total of 20 times. When CSI was completed, 54 to 55.8 Gy was added to all patients with local tumor beds once a day, for a total of 1.8 Gy each time.[1] Patient demographic data, including sex, age, height, weight, primary tumor site, CSI dose stratification, risk stratification, and chemotherapy status, were obtained from the medical records system. BMI was calculated using the following formula: BMI = weight/height^2 (kg/m^2).

Continuous cessation of radiotherapy for ⩾ 5 days was defined as radiotherapy interruption. Data on radiotherapy continuity, including occurrence (excluding interruptions due to holidays and machine malfunctions), duration, and timing of interruptions, were obtained from the MOSAIQ Integration Platform 2.0 system.

During radiotherapy, routine blood tests were conducted weekly. Daily routine blood monitoring was initiated in cases of a significant decrease in blood parameters. Hemoglobin (Hb), neutrophil (NE), white blood cell (WBC), blood platelet (BLT), and lymphocyte (Lym) levels at each radiotherapy session were recorded. Hematological toxicity was graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events version 4.0, ranging from Grade 0 to 4. Bone marrow depression (BMD) severity grade was determined on the basis of the most severe toxicity level in terms of the Hb, NE, WBC, or BLT levels.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics 28.0. Nonnormally distributed samples are expressed as interquartile ranges Q2 (Q1, Q3), where Q1 is the lower quartile, Q2 is the median, and Q3 is the upper quartile. Spearman's correlation analysis determined correlations between radiotherapy interruption, hematological suppression, and various factors. Intergroup comparisons were conducted using independent sample nonparametric tests; the Mann-Whitney U test and Kruskal-Wallis H test were performed for two-group and multigroup comparisons, respectively. $P < .05$ was considered to indicate statistical significance.

Results

General information

Patients with MB admitted from August 2019 to December 2023 were screened on the basis of the inclusion and exclusion criteria. A total of 87 patients (59 males and 28 females) were included. Their ages ranged from 2 to 30 years (mean, 9.69 years; median, 8 years). The BMI of the patients ranged from 10.22 to 23.92, and none were classified as overweight or obese. The chemotherapy regimens of the enrolled patients were Cyclophosphamide (CTX) + Cisplatin (DDP) + Vincristine (VCR) combined with Lomustine (CCNU) + DDP + VCR.[1] Patients were categorized into the HT, IMRT, and 3D-CRT groups on the basis of the treatment modality. Patient demographics are detailed in Table 1.

Radiotherapy continuity and bone marrow suppression

Radiotherapy continuity. Among the enrolled patients, 22.99% (20 out of 87) experienced interruptions in radiotherapy. The median duration of interruptions was 6.5 (5-8) days, occurring on the 12th (7.5, 14.75) radiotherapy session.

Bone marrow suppression. Patients with Grade 1 to 4 bone marrow suppression accounted for 14.9% (13 out of 87), 43.7% (38 out of 87), 32.2% (28 out of 87), and 5.7% (5 out of 87) of the total patients, respectively. The timing of occurrence was as follows: sixth (5, 10.5), eighth (6, 12), ninth (7, 13.5), and eighth (7.5, 13.5) radiotherapy sessions. Figure 1 shows that the incidences of Grade 1 to 4 hematological toxicity in terms of Hb, NE, WBC, and BLT among patients were 28.7%, 12.6%, 1.1%, 0%, 20.7%, 29.9%, 12.6%, 3.4%, 17.2%, 43.7%, 28.7%, and 4.6% and 63.2%, 19.5%, 11.5%, 4.6%, and 1.1%, respectively. The timing of occurrence was (8 [7, 12], 8 [7, 13], 0, 0), (10.5 [7, 12], 8 [7, 10], 9 [7, 17], 10 [7, 10]), (6.5 [5, 12.25], 8 [6.75, 12], 9 [7,

Table 1. Basic information of 87 patients with medulloblastoma.

PATIENT CHARACTERISTICS	N
Gender	
Male	59 (67.82%)
Female	28 (32.18%)
Tumor primary site	
Fourth ventricle	29 (33.33%)
Vermis of cerebellum	58 (66.67%)
Risk stratification and CSI dose stratification	
High risk (36 Gy)	39 (44.83%)
Standard risk (23.4 Gy)	48 (55.17)
Treatment modality	
HT	47 (54.02%)
IMRT	14 (16.09%)
3D-CRT	26 (29.89%)

Abbreviations: CSI, craniospinal irradiation; 3D-CRT, three-dimensional conformal radiation therapy; HT, helical tomotherapy; IMRT, intensity-modulated radiotherapy.

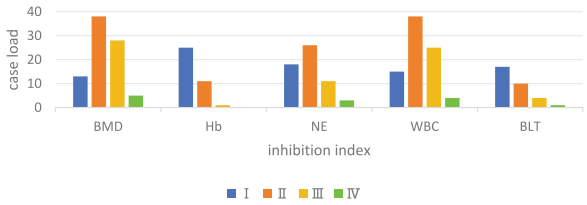

Figure 1. Distribution of bone marrow suppression and hematological toxicity grades in 87 patients. BLT indicates blood platelet; BMD, bone marrow depression; Hb, hemoglobin; NE, neutrophil; WBC, white blood cell.

13.5], 8 [7.25, 11]), and (12 [10, 13], 11.5 [10.75, 13.25], 9.5 [7, 15.75], 0) radiotherapy sessions, as shown in Figure 2.

Factors affecting radiotherapy continuity and bone marrow suppression. Radiotherapy interruption was weakly correlated with age and treatment modality (r=–0.266 and –0.251, respectively, both with P values < .05). However, there was no correlation between the duration of interruption and the factors included in the analysis. The timing of interruption was weakly correlated with the dose and treatment modality (r=0.515 and 0.476, both with P values < .05). Bone marrow suppression severity was weakly correlated with age, BMI, and treatment modality (r=–0.396, P< .001; r=–0.298, P=.005; and r=–0.226, P=.013, respectively). The above-related variables were included in the multivariate logistic analysis, which revealed that treatment modality was an independent predictor of radiotherapy interruption. The risk of radiotherapy interruption using HT and IMRT was 4.17 and 2.73 times greater than that using 3D-CRT, respectively. The 95% confidence

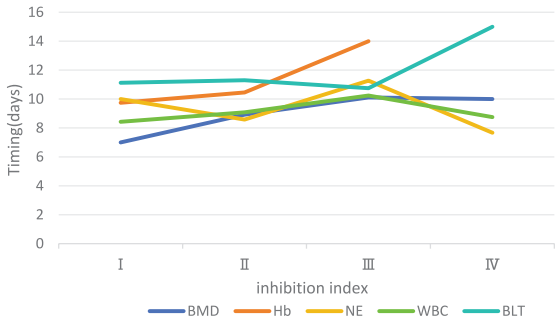

Figure 2. Timing of bone marrow suppression and hematological toxicity occurrence in 87 patients. BLT indicates blood platelet; BMD, bone marrow depression; Hb, hemoglobin; NE, neutrophil; WBC, white blood cell.

intervals were 0.84 to 20.73 and 0.39 to 19.33, respectively. Neither the dose nor the treatment modality was an independent predictor of the timing of radiotherapy interruption. Age was an independent predictor of bone marrow suppression severity, and with increasing age, mild bone marrow increased the probability of bone marrow occurrence.

The Hb-related hematological toxicity was weakly correlated with age, BMI, and dose (r=–0.39, P< .001; r=–0.212, P=.049; and r=0.263, P=.014, respectively) but moderately correlated with treatment modality (r=–0.493, P< .05). The NE-related hematological toxicity was weakly correlated with age (r=–0.269, P=.012) and BMI (r=–0.17, P=.044). The WBC-related hematological toxicity was weakly correlated with age, sex, BMI, and treatment modality (r=–0.354, P< .001; r=0.25, P=.02; r=–0.339, P< .001; and r=–0.213, P=.048, respectively). The BLT-related hematological parameters were weakly correlated with dose and treatment modality (r=0.048, P< .05; and r=–0.298, P< .05, respectively). Lym-related hematological toxicity was moderately associated with age and BMI (r= –0.404, P< .001; and r= –0.501, P< .001, respectively) and weakly associated with risk stratification and treatment technique (r=0.240, P< .05; and r= –0.376, P< .05, respectively).

Impact of various factors on radiotherapy continuity and bone marrow suppression

Effects of different treatment modalities on radiotherapy continuity and bone marrow suppression. The 87 patients were divided into three groups on the basis of treatment modality: HT (47), IMRT (14), and 3D-CRT (26). Table 2 summarizes the impacts of different treatment modalities on bone marrow suppression and hematological toxicity. There was no significant difference in treatment continuity between the HT, IMRT, and 3D-CRT groups (H=5.507, 5.91; P> .05 for all). However, bone marrow suppression severity differed significantly among the HT, IMRT, and 3D-CRT groups (H=7.461; P=.024). Compared with the 3D-CRT group, the HT group presented more severe suppression. The timing of bone marrow suppression onset differed among the three groups, with durations of 8

Table 2. Impact of different treatment modalities on bone marrow suppression and hematological toxicity in 87 patients with medulloblastoma, Q2 (Q1, Q3).

		HT (A) N = 47	IMRT (B) N = 14	3D-CRT (C) N = 26	*H*	*P*	PAIRWISE COMPARISON		
							A:B	A:C	B:C
The timing of the most severe suppression occurrence (days)	BMD	8 (7, 12)	10 (7.5, 12.5)	6 (5.5, 9.5)	8.496	.014	0.417	0.014	0.011
The level of suppression (graded)	BMD	3 (2, 3)	3 (2, 3)	2 (1, 2)	7.461	.024	0.894	0.008	0.067
	WBC	2 (2, 3)	2 (2, 3)	2 (1, 2)	5.035	.081			
	BLT	1 (0, 1)	0 (0, 1)	0 (0, 0)	7.756	.021	0.102	0.009	0.662
	Hb	1 (0, 1)	0 (0, 1)	0 (0, 0)	21.132	0	0.024	0.067	0.003
	Lym	3 (2, 3)	2 (1.75, 3)	2 (1, 3)	12.192	.002	0.049	< 0.01	0.400

Abbreviations: BMD, bone marrow depression; 3D-CRT, three-dimensional conformal radiation therapy; Hb, hemoglobin; HT, helical tomotherapy; IMRT, intensity-modulated radiotherapy; Lym, lymphocyte; WBC, white blood cell.

Table 3. Timing of bone marrow suppression and hematological toxicity in 87 patients with medulloblastoma stratified by sex, Q2 (Q1, Q3).

GROUP	BMD	HB	NE	WBC	BLT
Male	7 (6, 12)	10 (7, 12)	7 (6, 14)	8 (6, 12)	12 (7, 13)
Female	11.5 (7.75, 14.75)	13.5 (7.75, 15)	11 (8, 12.25)	11.5 (7.75, 14.75.)	12.5 (10.75, 14.75)

Abbreviations: BLT, blood platelet; BMD, bone marrow depression; Hb, hemoglobin; NE, neutrophil; WBC, white blood cell.

(7, 12), 10 (7.5, 12.5), and 6 (5.5, 9.5) days for the HT, IMRT, and 3D-CRT groups, respectively ($H = 8.496$, $P = .014$). Bone marrow suppression onset occurred later in both the HT and IMRT groups than in the 3D-CRT group. The groups differed significantly between Hb- and BLT-related hematological toxicity ($H = 21.132, 7.756$; $P = 0, .021$). The HT group presented the most Hb-related hematological toxicity, followed by the IMRT and 3D-CRT groups. In addition, the HT group exhibited more severe BLT-related toxicity than did the 3D-CRT group. Treatment modality did not impact WBC-related toxicity ($H = 5$, $P = .081$). Lym-related toxicity in the HT group was more severe than that in the IMRT and 3D-CRT groups ($H = 12.192$; $P = .002$).

Impact of different doses on hematological toxicity. The 87 patients were divided into two groups on the basis of radiation dose: 23.4 Gy (48 patients) and 36 Gy (39 patients). The Hb- and BLT-related toxicity levels in the 36 Gy group were significantly greater than those in the 23.4 Gy group ($Z = -2.443$, $P = .015$; $Z = -2.036$, $P = .042$). The timing of Hb-related toxicity onset was 8 (7, 12) sessions for the 23.4 Gy group and 11.5 (7, 14.75) for the 36 Gy group, whereas that for BLT-related toxicity was 7 (6, 9) sessions for the 23.4 Gy group and 10 (7, 13.5) for the 36 Gy group.

Effects of sex on the timing of severe bone marrow suppression and hematological toxicity. The patients were divided into male (59 patients) and female (28 patients) groups. The age of the male group was 8 (6, 3) years, and the age of the female group was 9 (6.25, 10) years. There was no significant difference in age between the two groups ($Z = -0.059$, $P > .05$). There were no correlations between sex, bone marrow suppression severity, or hematological toxicity level. However, male patients experienced severe bone marrow suppression and hematological toxicity earlier than female patients did (see Table 3).

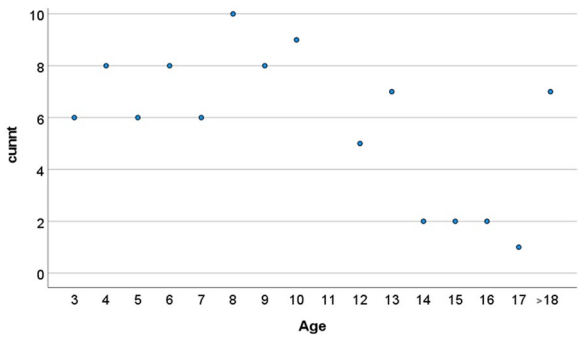

Figure 3. Scatter plot of the age distribution of the 87 patients.

Effects of different age distributions on radiotherapy continuity and bone marrow suppression. The age distribution of the 87 patients is shown in Figure 3. According to the Chinese national standard "Standards for Physical Development of Children" (GB 21521–2010), children aged less than or equal to 6 years were defined as children and those aged more than

6 years were defined as adolescents. The patients were divided into a pediatric group (28 patients) and an adolescent group (59 patients). The rate of interruption was greater in children than in adolescents (46.2% [13 out of 28] vs 11.9% [7 out of 59], $Z = -3.559$, $P < .05$). In terms of the severity of bone marrow suppression, the children and adolescents had Grades 3 (2, 3) and 2 (2, 3) bone marrow suppression, respectively, and the difference between the two groups was greater ($Z = -3.681$, $P < .05$).

Discussion

Treatment interruption and severe hematological suppression can significantly impact clinical outcomes in patients with MB.[1] In this study, 22.99% of patients experienced treatment interruptions during CSI for MB, whereas 96.55% (84 out of 87) experienced varying degrees of bone marrow suppression.

Multiple studies have reported that the continuity of CSI for MB is poor, often leading to treatment interruptions, with bone marrow suppression as a primary contributing factor. Yang et al[5] reported that among 82 patients who underwent CSI for MB, 21.98% experienced treatment interruptions. Similarly, Liu et al[3] reported that 25% of patients who underwent CSI with HT experienced treatment interruptions. In our study, 22.99% of patients experienced treatment interruptions, which is consistent with the findings of these previous studies. In addition, our study further analyzed the duration and timing of interruptions. We found that CSI with HT was associated with more severe bone marrow suppression than that with 3D-CRT, which is consistent with the findings of Liu et al.[3] Further analysis showed that the risks of radiotherapy interruption with HT and IMRT were 4.17 and 2.73 times greater than those with 3D-CRT, respectively. Therefore, patients with CSI using HT deserve our attention.

This study further examined the factors influencing bone marrow suppression and revealed that hematological toxicity was most severe in the HT group, followed by the IMRT group, and was least severe in the 3D-CRT group. Differences in dose distributions among various treatment modalities may influence the severity of hematological toxicity. For certain critical organs, the $D_{(V80)}$ value is greater with HT than with 3D-CRT.[8] In addition, low-dose radiation exposure to normal tissues may be greater with HT,[9] and IMRT may deliver a higher radiation dose to the spinal cord than 3D-CRT does.[10]

Yang et al[11] reported that a whole-spinal cord irradiation dose exceeding 30 Gy did not affect bone marrow suppression. We found that patients receiving a dose of 23.4 Gy during radiotherapy exhibited lower degrees of bone marrow suppression and hematological toxicity than those receiving a dose of 36 Gy. The possible reason is that Hb, PLT, and Lym are sensitive to radiotherapy,[12-14] suggesting that we should focus on the above three blood images when studying CSI-related hematological toxicity.

As shown in Figure 2, most of the most severe myelosuppression and hematological toxicity occurred in the middle and posterior segments after radiotherapy, which is consistent with previous findings.[15] As shown in Table 3, male patients had an earlier onset of highest-grade bone marrow suppression and hematological toxicity than female patients. This contradicts the results of Zhang et al,[15] who suggested that sex did not affect bone marrow suppression. This difference may be attributed to differences in the included diseases. Our study including patients with MBs did not specify the disease information of the included patients.

A previous study[16,17] indicated that younger patients tend to receive more radiation exposure to the vertebrae during radiotherapy because of the greater proportion of the spine in their skeleton, leading to more pronounced acute hematological toxicity. In agreement with these findings, our study revealed a negative correlation between age and bone marrow suppression severity and hematological toxicity, as indicated by Hb, NE, WBC, and Lym levels, and that children have a greater risk of radiotherapy continuity and a greater degree of bone marrow suppression than adolescents; therefore, monitoring hematological changes in younger patients is highly important. Furthermore, we observed a negative correlation between BMI and bone marrow suppression severity and hematological toxicity in terms of Hb, NE, WBC, and Lym levels, indicating that patients with a lower BMI are more prone to bone marrow suppression.

Owing to ongoing long-term follow-up and incomplete data, the effects of hematological toxicity and radiotherapy interruption on patient prognosis have not been thoroughly analyzed and are the focus of further research. Moreover, this study has shortcomings, such as the small number of cases and the single-center nature of the study. Follow-up multicenter studies should be carried out to clarify the continuity of CSI for MB and the situation of myelosuppression.

Conclusions

During radiotherapy for MB involving the entire brain and spinal cord, it is crucial to monitor hematological changes promptly in patients, especially in the middle and posterior segments, to prevent severe bone marrow suppression. Furthermore, treatment for HT, male sex, younger age, and lower BMI are indicators of increased clinical attention.

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Author Contributions

Huilang He, Feng Chi, and Senkui Xu made a substantial contribution to the concept or design of the work. Zongtai Li, Hui Liu, and Zhiyue Lin drafted the article or revised it critically for important intellectual content. Runnan Xiao, Wenlong Zhu, Chuyan Lin, and Jiaxiu Luo were involved in the acquisition, analysis, or interpretation of data. All authors read and approved the final article. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

Consent for Publication

Not applicable.

Data Availability

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Sun Yat-sen University Cancer Center (approval no. B2023–608–01) in accordance with the Declaration of Helsinki. All methods were carried out in accordance with relevant guidelines and regulations. This study has obtained the exemption of patient informed consent from the ethics committee of Sun Yat-sen University.

ORCID iD

Huilang He https://orcid.org/0000-0001-7353-2241

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